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(54) Title: AUGMENTED COGNITIVE TRAINING

(57) Abstract: The present invention provides methods of therapy of cognitive deficits associated with a central nervous system disorder or condition, methods of enhancing cognitive performance and methods for repeated stimulation of neuronal activity or a pattern of neuronal activity, such as that underlying a specific neuronal circuit(s). The methods comprise combining cognitive training protocols and a general administration of CREB pathway-enhancing agents.

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AUGMENTED COGNITIVE TRAINING

BACKGROUND OF THE INVENTION

An estimated 4 to 5 million Americans (about 2% of all ages and 15% of those older than age 65) have some form and degree of cognitive failure. Cognitive failure (dysfunction or loss of cognitive functions, the process by which knowledge is acquired, retained and used) commonly occurs in association with central nervous system (CNS) disorders or conditions, including age-associated memory impairment, delirium (sometimes called acute confusional state), dementia (sometimes classified as Alzheimer's or non-Alzheimer's type), Alzheimer's disease, Parkinson's disease, Huntington's disease (chorea), cerebrovascular disease (e.g., stroke, ischemia), affective disorders (e.g., depression), psychotic disorders (e.g., schizophrenia, autism (Kanner's Syndrome)), neurotic disorders (e.g., anxiety, obsessive-compulsive disorder), attention deficit disorder (ADD), subdural hematoma, normal-pressure hydrocephalus, brain tumor, head or brain trauma.

Cognitive dysfunction is typically manifested by one or more cognitive deficits, which include memory impairment (impaired ability to learn new information or to recall previously learned information), aphasia (language/speech disturbance), apraxia (impaired ability to carry out motor activities despite intact motor function), agnosia (failure to recognize or identify objects despite intact sensory function), disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting).

Cognitive dysfunction causes significant impairment of social and/or occupational functioning, which can interfere with the ability of an individual to perform activities of daily living and greatly impact the autonomy and quality of life of the individual.

Cognitive training protocols are generally employed in rehabilitating individuals who have some form and degree of cognitive dysfunction. For example, cognitive training protocols are commonly employed in stroke rehabilitation and in

age-related memory loss rehabilitation. Because multiple training sessions are often required before an improvement or enhancement of a specific aspect of cognitive performance (ability or function) is obtained in the individuals, cognitive training protocols are often very costly and time-consuming.

SUMMARY OF THE INVENTION

The present invention relates to a novel methodology, also referred to herein as augmented cognitive training (ACT), which can either (1) rehabilitate various forms of cognitive dysfunction more efficiently than any current method or (2) enhance normal cognitive performance (ability or function). ACT can be applied for any aspect of brain function that shows a lasting performance gain after cognitive training. Accordingly, ACT can be used in rehabilitating an animal with some form and degree of cognitive dysfunction or in enhancing (improving) normal cognitive performance in an animal. ACT can also be used to exercise appropriate neuronal circuits to fine-tune the synaptic connections of newly acquired, transplanted stem cells that differentiate into neurons.

As described herein, ACT comprises two indivisible parts: (1) a specific training protocol for each brain (cognitive) function and (2) administration of cyclic AMP response element binding protein (CREB) pathway-enhancing drugs. This combination can augment cognitive training by reducing the number of training sessions required to yield a performance gain relative to that obtained with cognitive training alone or by requiring shorter or no rest intervals between training sessions to yield a performance gain. This combination can also augment cognitive training by reducing the duration and/or number of training sessions required for the induction in a specific neuronal circuit(s) of a pattern of neuronal activity or by reducing the duration and/or number of training sessions or underlying pattern of neuronal activity required to induce CREB-dependent long-term structural/function (i.e., long-lasting) change among synaptic connections of the neuronal circuit. In this manner, ACT can improve the efficiency of existing cognitive training protocols, thereby yielding significant economic benefit.

For example, cognitive training protocols are employed in treating patients with depression (monopolor) and/or phobias to help them unlearn pathological responses associated with the depression and/or phobia(s) and learn appropriate behavior. Administration of a CREB pathway-enhancing drug in conjunction with cognitive training reduces the time and/or number of training sessions required to yield a gain in performance in these patients. As such, overall treatment is accomplished in a shorter period of time.

Similarly, cognitive training protocols are employed in treating patients with autism to help them unlearn pathological responses and to learn appropriate behavior. Administration of a CREB pathway-enhancing drug in conjunction with cognitive training reduces the time and/or number of training sessions required to yield a gain in performance in these patients.

Cognitive training protocols (e.g., physical therapy, bio-feedback methods) are employed in rehabilitating stroke patients (stroke rehabilitation), particularly rehabilitating impaired or lost sensory-motor function(s). Administration of a CREB pathway-enhancing drug in conjunction with cognitive training reduces the time and/or number of training sessions required to yield a gain in performance in these patients. Faster and more efficient recovery of lost cognitive function(s) are expected as a result.

Cognitive training protocols (e.g., massed training, spaced training) are employed in learning a new language or in learning to play a new musical instrument. Administration of a CREB pathway-enhancing drug in conjunction with cognitive training reduces the time and/or number of training sessions required to yield a gain in performance. As a result, less practice (training sessions) is required to learn the new language or to learn to play the new musical instrument.

Cognitive training protocols are employed in improving learning and/or performance in individuals with learning, language or reading disabilities. Administration of a CREB pathway-enhancing drug in conjunction with cognitive training reduces the time and/or number of training sessions required to yield a gain in performance in these individuals.

Cognitive training protocols are employed to exercise neuronal circuits in individuals to fine-tune synaptic connections of newly acquired, transplanted stem cells that differentiate into neurons. Administration of a CREB pathway-enhancing drug in conjunction with cognitive training reduces the time and/or number of training sessions required for the induction in (a) specific neuronal circuit(s) of a pattern of neuronal activity in these individuals.

Cognitive training protocols are employed for repeated stimulation of neuronal activity or a pattern of neuronal activity underlying (a) specific neuronal circuit(s) in individuals. Administration of a CREB pathway-enhancing drug in conjunction with cognitive training reduces the time and/or number of training sessions and/or underlying pattern of neuronal activity required to induce CREB-dependent long-term structure/function (i.e., long-lasting) change among synaptic connections of the neuronal circuit.

As a result of the present invention, methods of enhancing a specific aspect of cognitive performance in an animal (particularly a human or other mammal or vertebrate) in need thereof are provided herein comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to produce an improvement in performance of a cognitive task of interest by the animal. "Augmenting agents" are also referred to herein as "CREB pathway-enhancing drugs".

Methods are provided herein for treating a cognitive deficit associated with a central nervous system (CNS) disorder or condition in an animal in need of said treatment comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to produce an improvement in performance of a particular cognitive task by the animal. CNS disorders and conditions include age-associated memory impairment, neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease (chorea), other senile dementia), psychiatric diseases (e.g., depression, schizophrenia, autism, attention deficit disorder), trauma dependent loss of function (e.g., cerebrovascular diseases (e.g., stroke, ischemia),

brain tumor, head or brain injury), genetic defects (e.g., Rubinstein-Taybi syndrome, down syndrome) and learning disabilities.

Methods are also provided herein for therapy of a cognitive deficit associated with a CNS disorder or condition in an animal having undergone neuronal stem cell manipulation comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to stimulate or induce neuronal activity or a pattern of neuronal activity in the animal. By "neuronal stem cell manipulation" is meant that (1) exogenous neuronal stem cells are transplanted into the brain or spinal chord of an animal or (2) endogenous neuronal stem cells are stimulated or induced to proliferate in the animal.

Methods are provided herein for repeated stimulation of neuronal activity or a pattern of neuronal activity, such as that underlying a specific neuronal circuit(s), in an animal comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to stimulate or induce neuronal activity or a pattern of neuronal activity in the animal.

BRIEF DESCRIPTION OF THE DRAWING

The Figure is a schematic diagram illustrating a neuronal mechanism of brain plasticity, which forms the neurological basis for augmented cognitive training. Specific cognitive training protocols produce (experience-dependent) changes in neural activity of specific underlying neuronal circuits. This neural activity activates a biochemical process that modulates CREB-dependent gene expression. Downstream effectors of this transcription factor cascade then yield long-lasting structural and functional changes in synaptic connectivity of the circuit (i.e., long-term memory). This process of experience-dependent synaptic modification is ongoing in normal animals and usually requires multiple training sessions for most tasks. Augmentation of the CREB pathway during training will reduce the number of training sessions (or shorten the rest interval between them) required to produce the experience-dependent changes in synaptic structure and/or function.

DETAILED DESCRIPTION OF THE INVENTION

For many tasks in many species, including human, spaced training protocols (multiple training sessions with a rest interval between each) produce stronger, longer-lasting memory than massed training protocols (multiple training sessions with no rest interval in between). Behavior-genetic studies of Pavlovian olfactory learning in Drosophila have established that massed training produces a long-lasting memory that nevertheless decays away in at least four days, is not protein synthesis-dependent, is not disrupted by overexpression of a CREB-repressor transgene, and is disrupted in *radish* mutants (Tully, T. *et al.*, *Cell*, 79(1):35-47 (1994); and Yin, J.C. *et al.*, *Cell*, 79(1):49-58 (1994)). In contrast, spaced training produces a long-lasting memory that persists for at least seven days, is protein synthesis-dependent, is disrupted by overexpression of a CREB-repressor transgene and is normal in *radish* mutants (Tully, T. *et al.*, *Cell*, 79(1):35-47 (1994); and Yin, J.C. *et al.*, *Cell*, 79(1):49-58 (1994)). One day after spaced training, memory retention is composed of both the protein synthesis- and CREB-independent early memory (ARM) and the protein synthesis- and CREB-dependent long-term memory (LTM). Additional massed training is insufficient to induce LTM (Tully, T. *et al.*, *Cell*, 79(1):35-47 (1994); and Yin, J.C. *et al.*, *Cell*, 79(1):49-58 (1994)).

A growing body of evidence extends these results from invertebrates to mammals. For example, in *Aplysia*, molecular manipulations of CREB expression, similar to those in flies, suppress or enhance (i) LTM of a facilitatory electrophysiological response at a sensorimotor monosynapse in cell culture and (ii) the synaptic connections between sensory and motor neurons that are normally produced after spaced applications of the facilitatory stimulus (Bartsch, D. *et al.*, *Cell,* 83(6):979-992 (1995)). In rats, injections of antisense RNA oligonucleotides into hippocampus or amygdala block LTM formation of two different tasks that are dependent on activity in these anatomical regions, respectively (Guzowski, J.F. *et al.*, *Proc. Natl. Acad. Sci. USA*, 94(6):2693-2698 (1997); and Lamprecht, R. *et al.*, *J. Neurosci.*, 17(21):8443-8450 (1997)). In mice, LTM formation for both implicit and explicit tasks is defective in CREB mutant mice (Bourtchuladze, R. *et al.*, *Cell*, 79(1):59-68 (1994)).

Training of transgenic mice, carrying a CRE-dependent reporter gene (beta-galactosidase), in hippocampal-dependent contextual fear conditioning or passive avoidance tasks induces CRE-dependent reporter gene expression in areas CA1 and CA3 of the hippocampus. Training of these mice in an amygdala-dependent fear conditioning task induces CRE-dependent reporter gene expression in the amygdala, but not the hippocampus. Thus, training protocols that induce LTM formation also induce CRE-dependent gene transcription in specific anatomical areas of the mammalian brain (Impey, S. *et al., Nat. Neurosci.*, 1(7):595-601 (1998)).

With these animal models, three salient cases of LTM enhancement have been demonstrated. First, overexpression of a CREB-activator transgene abrogates the requirements for multiple, spaced training sessions and, instead, induces LTM formation after only one training session (which normally produces little or no memory retention 24 hours later (Yin, J.C. *et al., Cell*, 81(1):107-115 (1995)). Second, injection of a virally expressed CREB-activator transgene into rat amygdala also is sufficient to enhance memory after massed training for the fear-potentiated startle response, which abrogates the requirement for a rest interval in spaced training (Josselyn, S.A. *et al., Society for Neuroscience*, Vol. 24, Abstract 365.10 (1998)). Third, LTM formation in CREB-deficient mice (Bourtchuladze, R. *et al., Cell*, 79(1):59-68 (1994)) can form normally, if mutant mice are subjected to a different, spaced training protocol (Kogan, J.H. *et al., Curr. Biol.*, 7(1):1-11 (1997)).

CREB also appears involved in various forms of developmental and cellular plasticity in the vertebrate brain. For example, neuronal activity increases CREB activity in the cortex (Moore, A.N. *et al., J. Biol. Chem.*, 271(24):14214-14220 (1996)). CREB also mediates developmental plasticity in the hippocampus (Murphy, D.D. *et al., Proc. Natl. Acad. Sci. USA*, 94(4):1482-1487 (1997)), in the somatosensory cortex (Glazewski, S. *et al., Cereb. Cortex*, 9(3):249-256 (1999)), in the striatum (Liu, F.C. *et al., Neuron*, 17(6):1133-1144 (1996)), and in the visual cortex (Pham, T.A. *et al., Neuron*, 22(1):63-72 (1999)).

CREB appears to be affected in human neurodegenerative disease and brain injury. For example, CREB activation and/or expression is disrupted in Alzheimer's disease (Ikezu, T. *et al., EMBO J.*, 15(10):2468-2475 (1996); Sato, N. *et al.*,

Biochem. Biophys. Res. Commun., 232(3):637-642 (1997); and Yamamoto-Sasaki, M. *et al.*, *Brain. Res.*, 824(2):300-303 (1999). CREB activation and/or expression is also elevated after seizures or ischemia (Blendy, J.A. *et al.*, *Brain Res.*, 681(1-2):8-14 (1995); and Tanaka, K. *et al.*, *Neuroreport*, 10(11):2245-2250 (1999)). "Environmental enrichment" is neuroprotective, preventing cell death by acting through CREB (Young, D. *et al.*, *Nat. Med.*, 5(4):448-453 (1999)).

CREB functions during drug sensitivity and withdrawal. For example, CREB is affected by ethanol (Pandey, S.C. *et al.*, *Alcohol Clin. Exp. Res.*, 23(9):1425-1434 (1999); Constantinescu, A. *et al.*, *J. Biol. Chem.*, 274(38):26985-26991 (1999); Yang, X. *et al.*, *Alcohol Clin. Exp. Res.*, 22(2):382-390 (1998); Yang, X. *et al.*, *J. Neurochem.*, 70(1):224-232 (1998); and Moore, M.S. *et al.*, *Cell*, 93(6):997-1007 (1998)), by cocaine (Carlezon, W.A., Jr. *et al.*, *Science*, 282(5397):2272-2275 (1998)), by morphine (Widnell, K.L. *et al.*, *J. Pharmacol. Exp. Ther.*, 276(1):306-315 (1996)), by methamphetamine (Muratake, T. *et al.*, *Ann N. Y. Acad. Sci.*, 844:21-26 (1998)) and by cannabinoid (Calandra, B. *et al.*, *Eur. J. Pharmacol.*, 374(3):445-455 (1999); and Herring, A.C. *et al.*, *Biochem. Pharmacol.*, 55(7):1013-1023 (1998)).

A signal transduction pathway that can stimulate the CREB/CRE transcriptional pathway is the cAMP regulatory system. Consistent with this, mice lacking both adenylate cyclase 1 (AC1) and AC8 enzymes fail to learn (Wong S.T. *et al.*, *Neuron,* 23(4):787-798 (1999)). In these mice, administration of forskolin to area CA1 of the hippocampus restores learning and memory of hippocampal-dependent tasks. Furthermore, treatment of aged rats with drugs that elevate cAMP levels (such as rolipram and D1 receptor agonists) ameliorates an age-dependent loss of hippocampal-dependent memory and cellular long-term potentiation (Barad, M. *et al.*, *Proc. Natl. Acad. Sci. USA*, 95(25):15020-15025 (1998)). These latter data suggest that a cAMP signaling is defective in learning-impaired aged rats (Bach, M.E. *et al.*, *Proc. Natl. Acad. Sci. USA*, 96(9):5280-5285 (1999)).

The present invention relates to a novel methodology, also referred to herein as augmented cognitive training (ACT), which can (1) rehabilitate various forms of cognitive dysfunction or (2) enhance normal cognitive performance. ACT acts via a

general molecular mechanism of synaptic plasticity, which apparently converts the biochemical effect of a newly acquired experience into a long-lasting structural change of the synapse. ACT can be applied for any aspect of brain function that shows a lasting performance gain after cognitive training. Accordingly, ACT can be used in rehabilitating an animal with any form of cognitive dysfunction or in enhancing or improving any aspect of normal cognitive performance in an animal.

A growing body of evidence suggests that neurons continue to proliferate in the adult brain (Arsenijevic, Y. *et al., Exp. Neurol.*, 170: 48-62 (2001); Vescovi, A. L. *et al., Biomed. Pharmacother.*, 55:201-205 (2001); Cameron, H. A. and McKay, R. D., *J. Comp. Neurol.*, 435:406-417 (2001); and Geuna, S. *et al., Anat. Rec.*, 265:132-141 (2001)) and that such proliferation is in response to various experiences (Nilsson, M. *et al., J. Neurobiol.*, 39:569-578 (1999); Gould, E. *et al., Trends Cogn. Sci.*, 3:186-192 (1999); Fuchs, E. and Gould, E., *Eur. J. Neurosci.*,12: 2211-2214 (2000); Gould, E. *et al., Biol. Psychiatry*, 48:715-720 (2000); and Gould, E. *et al., Nat. Neurosci.*, 2:260-265 (1999)). Experimental strategies now are underway to transplant neuronal stem into adult brain for various therapeutic indications (Kurimoto, Y. *et al., Neurosci. Lett.*, 306:57-60 (2001); Singh, G., *Neuropathology*, 21:110-114 (2001); and Cameron, H. A. and McKay, R. D., *Nat. Neurosci.*, 2:894-897 (1999)). Much already is known about neurogenesis in embryonic stages of development (Saitoe, M. and Tully, T., "Making connections between synaptic and behavioral plasticity in Drosophila", In *Toward a Theory of Neuroplasticity*, J. McEachern and C. Shaw, Eds. (New York: Psychology Press.), pp. 193-220 (2000)). Neuronal differentiation, neurite extension and initial synaptic target recognition all appear to occur in an activity-independent fashion. Subsequent synaptogenesis and synaptic growth, however, then requires ongoing neuronal activity to fine-tune synaptic connections in a functionally relevant manner. These findings suggest that functional (final) integration of transplanted neural stem cells require neuronal activity. Thus, ACT can be used to exercise appropriate neuronal circuits to fine-tune the synaptic connections of newly acquired, transplanted stem cells that differentiate into neurons. By "exercise appropriate neuronal circuit(s)" is meant the induction in the appropriate neuronal circuit(s) of a pattern of neuronal

activity, which corresponds to that produced by a particular cognitive training protocol. The cognitive training protocol can be used to induce such neuronal activity. Alternatively, neuronal activity can be induced by direct electrical stimulation of the neuronal circuitry. "Neuronal activity" and "neural activity" are used interchangeably herein.

ACT comprises a specific training protocol for each brain function and a general administration of CREB pathway-enhancing drugs. The training protocol (cognitive training) induces neuronal activity in specific brain regions and produces improved performance of a specific brain (cognitive) function. CREB pathway-enhancing drugs, also referred to herein as augmenting agents, enhance CREB pathway function, which is required to consolidate newly acquired information into LTM. By "enhance CREB pathway function" is meant the ability to enhance or improve CREB-dependent gene expression. CREB-dependent gene expression can be enhanced or improved by increasing endogenous CREB production, for example by directly or indirectly stimulating the endogenous gene to produce increased amounts of CREB, or by increasing functional (biologically active) CREB. See, e.g., U.S. Patent No. 5,929,223; U.S. Patent No. 6,051,559; and International Publication No. WO9611270 (published April 18, 1996), which references are incorporated herein in their entirety by reference. Administration of CREB pathway-enhancing drugs decreases the training needed to yield a performance gain relative to that yielded with training alone. In particular, ACT can enhance cognitive training by reducing the number of training sessions required to yield a performance gain relative to that yielded with cognitive training alone or by requiring shorter or no rest intervals between training sessions to yield a performance gain. In this manner, ACT can improve the efficiency of cognitive training techniques, thereby yielding significant economic benefit. By "performance gain" is meant an improvement in an aspect of cognitive performance.

The invention provides methods for enhancing a specific aspect of cognitive performance in an animal (particularly in a human or other mammal or vertebrate) in need thereof comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions

sufficient to produce an improvement in performance of a particular cognitive task by the animal.

Training can comprise one or multiple training sessions and is training appropriate to produce an improvement in performance of the cognitive task of interest. For example, if an improvement in language acquisition is desired, training would focus on language acquisition. If an improvement in ability to learn to play a musical instrument is desired, training would focus on learning to play the musical instrument. If an improvement in a particular motor skill is desired, training would focus on acquisition of the particular motor skill. The specific cognitive task of interest is matched with appropriate training.

The invention also provides methods for repeated stimulation of neuronal activity or a pattern of neuronal activity, such as that underlying (a) specific neuronal circuit(s), in an animal comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to stimulate or induce neuronal activity or a pattern of neuronal activity in the animal. In this case, training is training appropriate to stimulate or induce neuronal activity or a pattern of neuronal activity in the animal.

By "multiple training sessions" is meant two or more training sessions. The augmenting agent can be administered before, during or after one or more of the training sessions. In a particular embodiment, the augmenting agent is administered before and during each training session. Treatment with augmenting agent in connection with each training session is also referred to as the "augmenting treatment". By "training" is meant cognitive training.

Cognitive training protocols are known and readily available in the art. See for example, Karni, A. and Sagi, D., "Where practice makes perfect in text discrimination: evidence for primary visual cortex plasticity", *Proc. Natl. Acad. Sci. USA*, 88:4966-4970 (1991); Karni, A. and Sagi, D., "The time course of learning a visual skill", *Nature*, 365:250-252 (1993); Kramer, A.F. *et al.*, "Task coordination and aging: explorations of executive control processes in the task switching paradigm", *Acta Psychol. (Amst.)*, 101:339-378 (1999); Kramer, A.F. *et al.*, "Training for executive control: Task coordination strategies and aging", *In Aging*

and Skilled Performance: Advances In Theory and Applications, W. Rogers *et al.*, eds. (Hillsdale, N.J.: Erlbaum) (1999); Rider, R.A. and Abdulahad, D.T., "Effects of massed versus distributed practice on gross and fine motor proficiency of educable mentally handicapped adolescents", *Percept. Mot. Skills*, 73:219-224 (1991); Willis, S.L. and Schaie, K.W., "Training the elderly on the ability factors of spatial orientation and inductive reasoning", *Psychol. Aging*, 1:239-247 (1986); Willis, S.L. and Nesselroade, C.S., "Long-term effects of fluid ability training in old-old age", *Develop. Psychol.*, 26:905-910 (1990); Wek, S.R. and Husak, W.S., "Distributed and massed practice effects on motor performance and learning of autistic children", *Percept. Mot. Skills*, 68:107-113 (1989); Verhaehen, P. *et al.*, "Improving memory performance in the aged through mnemonic training: a meta-analytic study", *Psychol. Aging*, 7:242-251 (1992); Verhaeghen, P. and Salthouse, T.A., "Meta-analyses of age-cognition relations in adulthood: estimates of linear and nonlinear age effects and structural models", *Psychol. Bull.*, 122:231-249 (1997); Dean, C.M. *et al.*, "Task-related circuit training improves performance of locomotor tasks in chronic stroke: a randomized, controlled pilot trial", *Arch. Phys. Med. Rehabil.*, 81:409-417 (2000); Greener, J. *et al.*, "Speech and language therapy for aphasia following stroke", *Cochrane Database Syst. Rev.*, CD000425 (2000); Hummelsheim, H. and Eickhof, C., "Repetitive sensorimotor training for arm and hand in a patient with locked-in syndrome", *Scand. J. Rehabil. Med.*, 31:250-256 (1999); Johansson, B.B., "Brain plasticity and stroke rehabilitation. The Willis lecture", *Stroke*, 31:223-230 (2000); Ko Ko, C., "Effectiveness of rehabilitation for multiple sclerosis", *Clin. Rehabil.*, 13 (Suppl. 1):33-41 (1999); Lange, G. *et al.*, "Organizational strategy influence on visual memory performance after stroke: cortical/subcortical and left/right hemisphere contrasts", *Arch. Phys. Med. Rehabil.*, 81:89-94 (2000); Liepert, J. *et al.*, "Treatment-induced cortical reorganization after stroke in humans", *Stroke*, 31:1210-1216 (2000); Lotery, A.J. *et al.*, "Correctable visual impairment in stroke rehabilitation patients", *Age Ageing*, 29:221-222 (2000); Majid, M.J. *et al.*, "Cognitive rehabilitation for memory deficits following stroke" (Cochrane review), *Cochrane Database Syst. Rev.*, CD002293 (2000); Merzenich, M. *et al.*, "Cortical plasticity underlying perceptual, motor, and cognitive skill

development: implications for neurorehabilitation", *Cold Spring Harb. Symp. Quant. Biol.*, 61:1-8 (1996); Merzenich, M.M. *et al.*, "Temporal processing deficits of language-learning impaired children ameliorated by training", *Science*, 271:77-81 (1996); Murphy, E., "Stroke rehabilitation", *J. R. Coll. Physicians Lond.*, 33:466-468 (1999); Nagarajan, S.S. *et al.*, "Speech modifications algorithms used for training language learning-impaired children", *IEEE Trans. Rehabil. Eng.*, 6:257-268. (1998); Oddone, E. *et al.*, "Quality Enhancement Research Initiative in stroke: prevention, treatment, and rehabilitation", *Med.Care* 38:I92-I104 (2000); Rice-Oxley, M. and Turner-Stokes, L., "Effectiveness of brain injury rehabilitation", *Clin. Rehabil.*, 13(Suppl 1):7-24 (1999); Tallal, P. *et al.*, "Language learning impairments: integrating basic science, technology, and remediation", *Exp. Brain Res.*, 123:210-219 (1998); Tallal, P. *et al.*, "Language comprehension in language-learning impaired children improved with acoustically modified speech", *Science*, 271:81-84 (1996), which references are incorporated herein in their entirety by reference.

As used herein, the term "animal" includes mammals, as well as other animals, vertebrate and invertebrate (e.g., birds, fish, reptiles, insects (e.g., Drosophila species), mollusks (e.g., Aplysia). The terms "mammal" and "mammalian", as used herein, refer to any vertebrate animal, including monotremes, marsupials and placental, that suckle their young and either give birth to living young (eutharian or placental mammals) or are egg-laying (metatharian or nonplacental mammals). Examples of mammalian species include humans and primates (e.g., monkeys, chimpanzees), rodents (e.g., rats, mice, guinea pigs) and ruminents (e.g., cows, pigs, horses).

The animal can be an animal with some form and degree of cognitive dysfunction or an animal with normal cognitive performance (i.e., an animal without any form of cognitive failure (dysfunction or loss of any cognitive function)).

Cognitive dysfunction, commonly associated with brain dysfunction and central nervous system (CNS) disorders or conditions, arises due to heredity, disease, injury and/or age. CNS disorders and conditions associated with some form and degree of cognitive failure (dysfunction) include, but are not limited to the following:

1) age-associated memory impairment;

2) neurodegenerative disorders, such as delirium (acute confusional state); dementia, including Alzheimer's disease and non-Alzheimer's type dementias, such as, but not limited to, Lewy body dementia, vascular dementia, Binswanger's dementia (subcortical arteriosclerotic encephalopathy), dementias associated with Parkinson's disease, progressive supranuclear palsy, Huntington's disease (chorea), Pick's disease, normal-pressure hydrocephalus, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease, neurosyphilis (general paresis) or HIV infection, frontal lobe dementia syndromes, dementias associated with head trauma, including dementia pugilistica, brain trauma, subdural hematoma, brain tumor, hypothyroidism, vitamin B_{12} deficiency, intracranial radiation; other neurodegenerative disorders;

3) psychiatric disorders, including affective disorders (mood disorders), such as, but not limited to, depression, including depressive pseudodementia; psychotic disorders, such as, but not limited to, schizophrenia and autism (Kanner's Syndrome); neurotic disorders, such as, but not limited to, anxiety and obsessive-compulsive disorder; attention deficit disorder;

4) trauma-dependent loss of cognitive function, such as, but not limited to that associated with (due to), cerebrovascular diseases, including stroke and ischemia, including ischemic stroke; brain trauma, including subdural hematoma and brain tumor; head injury;

5) disorders associated with some form and degree of cognitive dysfunction arising due to a genetic defect, such as, but not limited to, Rubinstein-Taybi syndrome and down syndrome;

6) learning, language or reading disabilities, particularly in children. By "learning disabilities" is meant disorders of the basic psychological processes that affect the way an individual learns. Learning disabilities can cause difficulties in listening, thinking, talking, reading, writing, spelling, arithmetic or combinations of any of the foregoing. Learning disabilities include perceptual handicaps, dyslexia and developmental aphasia.

The terms "cognitive performance" and "cognitive function" are art-recognized terms and are used herein in accordance with their art-accepted meanings. By "cognitive task" is meant a cognitive function. Cognitive functions include memory acquisition, visual discrimination, auditory discrimination, executive functioning, motor skill learning, abstract reasoning, spatial ability, speech and language skills and language acquisition. By "enhance a specific aspect of cognitive performance" is meant the ability to enhance or improve a specific cognitive or brain function, such as, for example, the acquisition of memory or the performance of a learned task. By "improvement in performance of a particular cognitive task" is meant an improvement in performance of a specific cognitive task or aspect of brain function relative to performance prior to training. For example, if after a stroke, a patient can only wiggle his or her toe, an improvement in performance (performance gain) in the patient would be the ability to walk, for example.

Accordingly, the invention also relates to methods of treating a cognitive deficit associated with a CNS disorder or condition in an animal (particularly in a human or other mammal or vertebrate) in need of said treatment comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to produce an improvement in performance of a particular cognitive task by the animal.

In one embodiment, the invention relates to a method of treating a cognitive deficit associated with age-associated memory impairment in an animal in need of said treatment comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to produce an improvement in performance by the animal of a cognitive task whose loss is associated with age-associated memory impairment.

In a second embodiment, the invention relates to a method of treating a cognitive deficit associated with a neurodegenerative disease (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, other senile dementia) in an animal in need of said treatment comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the

animal under conditions sufficient to produce an improvement in performance by the animal of a cognitive task whose deficit is associated with the neurodegenerative disease.

In a third embodiment, the invention relates to a method of treating a cognitive deficit associated with a psychiatric disease (e.g., depression, schizophrenia, autism, attention deficit disorder) in an animal in need of said treatment comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to produce an improvement in performance by the animal of a cognitive task whose deficit is associated with the psychiatric disease.

In a fourth embodiment, the invention relates to a method of treating a cognitive deficit associated with trauma dependent loss of cognitive function (e.g., cerebrovascular diseases (e.g., stroke, ischemia), brain tumor, head or brain injury) in an animal in need of said treatment comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to produce an improvement in performance by the animal of a cognitive task whose deficit is associated with trauma dependent loss of cognitive function.

In a fifth embodiment, the invention relates to a method of treating a cognitive deficit associated with a genetic defect (e.g., Rubinstein-Taybi syndrome, down syndrome) in an animal in need of said treatment comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to produce an improvement in performance by the animal of a cognitive task whose deficit is associated with a genetic defect.

The invention also relates to methods of therapy of a cognitive deficit associated with a CNS disorder or condition in an animal having undergone neuronal stem cell manipulation comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to stimulate or induce neuronal activity or a pattern of neuronal activity in the animal. By "neuronal stem cell manipulation" is

meant that (1) exogenous neuronal stem cells are transplanted into the brain or spinal chord of an animal or (2) endogenous neuronal stem cells are stimulated or induced to proliferate in the animal. Methods of transplanting neuronal stem cells into the brain or spinal chord of an animal are known and readily available in the art (see, e.g., Cameron, H. A. and McKay, R. D., *Nat. Neurosci.*, 2:894-897 (1999); Kurimoto, Y. *et al.*, *Neurosci. Lett.*, 306:57-60 (2001); and Singh, G., *Neuropathology*, 21:110-114 (2001)). Methods of stimulating or inducing proliferation of endogenous neuronal stem cells in an animal are known and readily available in the art (see, e.g., Gould, E. *et al.*, *Trends Cogn. Sci,*, 3:186-192 (1999); Gould, E. *et al.*, *Biol. Psychiatry*, 48:715-20 (2000); Nilsson, M. *et al*, *J. Neurobiol.*, 39:569-578 (1999); Fuchs, E. and Gould, E., *Eur. J. Neurosci.*, 12:2211-2214 (2000); and Gould, E. *et al.*, *Nat. Neurosci.*, 2:260-265 (1999)). The particular methods of transplanting neuronal stem cells into the brain or spinal chord of an animal and the particular methods of stimulating or inducing proliferation of endogenous neuronal stem cells in an animal are not critical to the practice of the invention.

The invention further relates to methods of improving or enhancing learning and/or performance in an animal with a learning, language or reading disability, or combinations of any of the foregoing, comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to produce an improvement in performance by the animal of a cognitive task associated with the disability in learning, language or reading performance.

Augmenting agents, as used herein, are compounds with pharmacological activity and include drugs, chemical compounds, ionic compounds, organic compounds, organic ligands, including cofactors, saccharides, recombinant and synthetic peptides, proteins, peptoids, nucleic acid sequences, including genes, nucleic acid products, and other molecules and compositions.

For example, augmenting agents can be cell permeant cAMP analogs (e.g, 8-bromo cAMP); activators of adenylate cyclase 1 (AC1) (e.g., forskolin); agents affecting G-protein linked receptor, such as, but not limited to adrenergic receptors

and opioid receptors and their ligands (e.g., phenethylamines); modulators of intracellular calcium concentration (e.g., thapsigargin, N-methyl-D-aspartate (NMDA) receptor agonists); inhibitors of the phosphodiesterases responsible for cAMP breakdown (e.g., rolipram (which inhibits phosphodiesterase 4), iso-buto-metho-xanthine (IBMX) (which inhibits phosphodiesterases 1 and 2)); modulators of protein kinases and protein phosphatases, which mediate CREB protein activation and CREB-dependent gene expression. Augmenting agents can be exogenous CREB, CREB analogs, CREB-like molecules, biologically active CREB fragments, CREB fusion proteins, nucleic acid sequences encoding exogenous CREB, CREB analogs, CREB-like molecules, biologically active CREB fragments or CREB fusion proteins.

Augmenting agents can also be CREB function modulators, or nucleic acid sequences encoding CREB function modulators. CREB function modulators, as used herein, have the ability to modulate CREB pathway function. By "modulate" is meant the ability to change (increase or decrease) or alter CREB pathway function.

Augmenting agents can be compounds which are capable of enhancing CREB function in the CNS. Such compounds include, but are not limited to, compounds which affect membrane stability and fluidity and specific immunostimulation. In a particular embodiment, the augmenting agent is capable of transiently enhancing CREB pathway function in the CNS.

CREB analogs, or derivatives, are defined herein as proteins having amino acid sequences analogous to endogenous CREB. Analogous amino acid sequences are defined herein to mean amino acid sequences with sufficient identity of amino acid sequence of endogenous CREB to possess the biological activity of endogenous CREB, but with one or more "silent" changes in the amino acid sequence. CREB analogs include mammalian CREM, mammalian ATF-1 and other CREB/CREM/ATF-1 subfamily members.

CREB-like molecule, as the term is used herein, refers to a protein which functionally resembles (mimics) CREB. CREB-like molecules need not have amino acid sequences analogous to endogenous CREB.

Biologically active polypeptide fragments of CREB can include only a part of the full-length amino acid sequence of CREB, yet possess biological activity. Such fragments can be produced by carboxyl or amino terminal deletions, as well as internal deletions.

Fusion proteins comprise a CREB protein as described herein, referred to as a first moiety, linked to a second moiety not occurring in the CREB protein. The second moiety can be a single amino acid, peptide or polypeptide or other organic moiety, such as a carbohydrate, a lipid or an inorganic molecule.

Nucleic acid sequences are defined herein as heteropolymers of nucleic acid molecules. The nucleic acid molecules can be double stranded or single stranded and can be a deoxyribonucleotide (DNA) molecule, such as cDNA or genomic DNA, or a ribonucleotide (RNA) molecule. As such, the nucleic acid sequence can, for example, include one or more exons, with or without, as appropriate, introns, as well as one or more suitable control sequences. In one example, the nucleic acid molecule contains a single open reading frame which encodes a desired nucleic acid product. The nucleic acid sequence is "operably linked" to a suitable promoter.

A nucleic acid sequence encoding a desired CREB protein, CREB analog (including CREM, ATF-1), CREB-like molecule, biologically active CREB fragment, CREB fusion protein or CREB function modulator can be isolated from nature, modified from native sequences or manufactured *de novo*, as described in, for example, Ausubel *et al., Current Protocols in Molecular Biology*, John Wiley & Sons, New York (1998); and Sambrook *et al., Molecular Cloning: A Laboratory Manual*, 2nd edition, Cold Spring Harbor University Press, New York. (1989). Nucleic acids can be isolated and fused together by methods known in the art, such as exploiting and manufacturing compatible cloning or restriction sites.

Typically, the nucleic acid sequence will be a gene which encodes the desired CREB protein, CREB analog, CREB-like molecule, CREB fusion protein or CREB function modulator. Such a gene is typically operably linked to suitable control sequences capable of effecting the expression of the CREB protein or CREB function modulator, preferably in the CNS. The term "operably linked", as used herein, is defined to mean that the gene (or the nucleic acid sequence) is linked to

control sequences in a manner which allows expression of the gene (or the nucleic acid sequence). Generally, operably linked means contiguous.

Control sequences include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable messenger RNA (mRNA) ribosomal binding sites and sequences which control termination of transcription and translation. In a particular embodiment, a recombinant gene (or a nucleic acid sequence) encoding a CREB protein, CREB analog, CREB-like molecule, biologically active CREB fragment, CREB fusion protein or CREB function modulator can be placed under the regulatory control of a promoter which can be induced or repressed, thereby offering a greater degree of control with respect to the level of the product.

As used herein, the term "promoter" refers to a sequence of DNA, usually upstream (5') of the coding region of a structural gene, which controls the expression of the coding region by providing recognition and binding sites for RNA polymerase and other factors which may be required for initiation of transcription. Suitable promoters are well known in the art. Exemplary promoters include the SV40 and human elongation factor (EFI). Other suitable promoters are readily available in the art (see, e.g., Ausubel *et al., Current Protocols in Molecular Biology,* John Wiley & Sons, Inc., New York (1998); Sambrook *et al., Molecular Cloning: A Laboratory Manual*, 2nd edition, Cold Spring Harbor University Press, New York (1989); and U.S. Patent No. 5,681,735).

Augmenting agents can enhance CREB pathway function by a variety of mechanisms. For example, an augmenting agent can affect a signal transduction pathway which leads to induction of CREB-dependent gene expression. Induction of CREB-dependent gene expression can be achieved, for example, via up-regulation of positive effectors of CREB function and/or down-regulation of negative effectors of CREB function. Positive effectors of CREB function include adenylate cyclases and CREB activators. Negative effectors of CREB function include cAMP phosphodiesterase (cAMP PDE) and CREB repressors.

An augmenting agent can enhance CREB pathway function by acting biochemically upstream of or directly acting on an activator or repressor form of a

CREB protein and/or on a CREB protein containing transcription complex. For example, CREB pathway function can be affected by increasing CREB protein levels transcriptionally, post-transcriptionally, or both transcriptionally and post-transcriptionally; by altering the affinity of CREB protein to other necessary components of the of the transcription complex, such as, for example, to CREB-binding protein (CBP protein); by altering the affinity of a CREB protein containing transcription complex for DNA CREB responsive elements in the promoter region; or by inducing either passive or active immunity to CREB protein isoforms. The particular mechanism by which an augmenting agent enhances CREB pathway function is not critical to the practice of the invention.

Augmenting agents can be administered directly to an animal in a variety of ways. In a preferred embodiment, augmenting agents are administered systemically. Other routes of administration are generally known in the art and include intravenous including infusion and/or bolus injection, intracerebroventricularly, intrathecal, parenteral, mucosal, implant, intraperitoneal, oral, intradermal, transdermal (e.g., in slow release polymers), intramuscular, subcutaneous, topical, epidural, etc. routes. Other suitable routes of administration can also be used, for example, to achieve absorption through epithelial or mucocutaneous linings. Particular augmenting agents can also be administered by gene therapy, wherein a DNA molecule encoding a particular therapeutic protein or peptide is administered to the animal, e.g., via a vector, which causes the particular protein or peptide to be expressed and secreted at therapeutic levels *in vivo*.

A vector, as the term is used herein, refers to a nucleic acid vector, e.g., a DNA plasmid, virus or other suitable replicon (e.g., viral vector). Viral vectors include retrovirus, adenovirus, parvovirus (e.g., adeno-associated viruses), coronavirus, negative strand RNA viruses such as orthomyxovirus (e.g., influenza virus), rhabdovirus (e.g., rabies and vesicular stomatitis virus), paramyxovirus (e.g. measles and Sendai), positive strand RNA viruses such as picornavirus and alphavirus, and double stranded DNA viruses including adenovirus, herpesvirus (e.g., Herpes Simplex virus types 1 and 2, Epstein-Barr virus, cytomegalovirus), and poxvirus (e.g., vaccinia, fowlpox and canarypox). Other viruses include Norwalk

virus, togavirus, flavivirus, reoviruses, papovavirus, hepadnavirus, and hepatitis virus, for example. Examples of retroviruses include: avian leukosis-sarcoma, mammalian C-type, B-type viruses, D-type viruses, HTLV-BLV group, lentivirus, spumavirus (Coffin, J.M., Retroviridae: The viruses and their replication, *In Fundamental Virology*, Third Edition, B.N. Fields, *et al.*, Eds., Lippincott-Raven Publishers, Philadelphia, 1996). Other examples include murine leukemia viruses, murine sarcoma viruses, mouse mammary tumor virus, bovine leukemia virus, feline leukemia virus, feline sarcoma virus, avian leukemia virus, human T-cell leukemia virus, baboon endogenous virus, Gibbon ape leukemia virus, Mason Pfizer monkey virus, simian immunodeficiency virus, simian sarcoma virus, Rous sarcoma virus and lentiviruses. Other examples of vectors are described, for example, in McVey et al., U.S. Patent No. 5,801,030, the teachings of which are incorporated herein by reference.

A nucleic acid sequence encoding a protein or peptide (e.g., CREB protein, CREB analog (including CREM, ATF-1), CREB-like molecule, biologically active CREB fragment, CREB fusion protein, CREB function modulator) can be inserted into a nucleic acid vector according to methods generally known in the art (see, e.g., Ausubel *et al.*, Eds., *Current Protocols in Molecular Biology,* John Wiley & Sons, Inc., New York (1998); Sambrook *et al.*, Eds., *Molecular Cloning: A Laboratory Manual*, 2nd edition, Cold Spring Harbor University Press, New York (1989)).

The mode of administration is preferably at the location of the target cells. In a particular embodiment, the mode of administration is to neurons.

Augmenting agents can be administered together with other components of biologically active agents, such as pharmaceutically acceptable surfactants (e.g., glycerides), excipients (e.g., lactose), stabilizers, preservatives, humectants, emollients, antioxidants, carriers, diluents and vehicles. If desired, certain sweetening, flavoring and/or coloring agents can also be added.

Augmenting agents can be formulated as a solution, suspension, emulsion or lyophilized powder in association with a pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, isotonic sodium chloride solution, dextrose solution, and 5% human serum albumin.

Liposomes and nonaqueous vehicles such as fixed oils can also be used. The vehicle or lyophilized powder can contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability (e.g., buffers and preservatives). The formulation can be sterilized by commonly used techniques. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences.

The dosage of augmenting agent administered to an animal is that amount required to effect a change in CREB-dependent gene expression, particularly in neurons. The dosage administered to an animal, including frequency of administration, will vary depending upon a variety of factors, including pharmacodynamic characteristics of the particular augmenting agent, mode and route of administration; size, age, sex, health, body weight and diet of the recipient; nature and extent of symptoms being treated or nature and extent of the cognitive function(s) being enhanced or modulated, kind of concurrent treatment, frequency of treatment, and the effect desired.

Augmenting agents can be administered in single or divided doses (e.g., a series of doses separated by intervals of days, weeks or months), or in a sustained release form, depending upon factors such as nature and extent of symptoms, kind of concurrent treatment and the effect desired. Other therapeutic regimens or agents can be used in conjunction with the present invention.

The teachings of all the articles, patents and patent applications cited herein are incorporated by reference in their entirety.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A method of treating a cognitive deficit associated with a central nervous system disorder or condition in an animal in need of said treatment comprising the steps of:
   (a) administering to said animal an augmenting agent which enhances CREB pathway function; and
   (b) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task whose deficit is associated with said central nervous system disorder or condition,

   whereby said cognitive deficit is treated.

2. A method of enhancing a specific aspect of cognitive performance in an animal, for example an animal in need thereof, comprising the steps of:
   (a) administering to said animal an augmenting agent which enhances CREB pathway function; and
   (b) training said animal under conditions sufficient to produce an improvement in performance of a specified cognitive task by said animal,

   whereby said specific aspect of cognitive performance is enhanced.

3. The method of Claim 1 or Claim 2 wherein said augmenting agent induces CREB-dependent gene expression.

4. The method of Claim 3 wherein (i) said augmenting agent up-regulates a positive effector of CREB pathway function, and optionally said positive effector of CREB pathway function is a CREB activator; or (ii) said augmenting agent down-regulates a negative effector of CREB pathway

function, and optionally said negative effector of CREB pathway function is a CREB repressor.

5. The method of Claim 1 or Claim 2 wherein said augmenting agent is a CREB functional modulator.

6. A method of treating a cognitive deficit associated with age-associated memory impairment in an animal in need of said treatment comprising the steps of:

(a) administering to said animal an augmenting agent which enhances CREB pathway function; and

(b) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task whose deficit is associated with age-associated memory impairment,

whereby said cognitive deficit is treated.

7. A method of treating a cognitive deficit associated with a neurodegenerative disease in an animal in need of said treatment comprising the steps of:

(a) administering to said animal an augmenting agent which enhances CREB pathway function; and

(b) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task whose deficit is associated with said neurodegenerative disease,

whereby said cognitive deficit is treated.

8. The method of Claim 7 wherein said neurodegenerative disease is selected from the group consisting of: delirium, dementia, Alzheimer's disease, Parkinson's disease and Huntington's disease.

9. A method of treating a cognitive deficit associated with a psychiatric disease in an animal in need of said treatment comprising the steps of:

(a) administering to said animal an augmenting agent which enhances CREB pathway function; and

(b) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task whose deficit is associated with said psychiatric disease,

whereby said cognitive deficit is treated.

10. The method of Claim 9 wherein said psychiatric disease is selected from the group consisting of: depression, schizophrenia, autism and attention deficit disorder.

11. A method of treating a cognitive deficit associated with cerebrovascular disease in an animal in need of said treatment comprising the steps of:

(a) administering to said animal an augmenting agent which enhances CREB pathway function; and

(b) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task whose deficit is associated with said cerebrovascular disease,

whereby said cognitive deficit is treated.

12. The method of Claim 11 wherein said cerebrovascular disease is selected from the group consisting of stroke and ischemia.

13. A method of treating a cognitive deficit associated with a trauma dependent loss of cognitive function in an animal in need of said treatment comprising the steps of:

(a) administering to said animal an augmenting agent which enhances CREB pathway function; and

(b) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task

whose deficit is associated with said trauma dependent loss of cognitive function,

whereby said cognitive deficit is treated.

14. The method of Claim 13 wherein said trauma dependent loss of function is selected from the group consisting of: head trauma and brain trauma.

15. A method of treating a cognitive deficit associated with a genetic defect in an animal in need of said treatment comprising the steps of:

(a) administering to said animal an augmenting agent which enhances CREB pathway function; and

(b) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task associated with said genetic defect,

whereby said cognitive deficit is treated.

16. The method of Claim 15 wherein said genetic defect is selected from the group consisting of: Rubinstein-Taybi syndrome and down syndrome.

17. A method of improving learning in an animal with a learning disability comprising the steps of:

(a) administering to said animal an augmenting agent which enhances CREB pathway function; and

(b) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task whose deficit is associated with said learning disability,

whereby learning is improved.

18. A method for repeated stimulation of neuronal activity or a pattern of neuronal activity in an animal comprising the steps of:

(a) administering to said animal an augmenting agent which enhances CREB pathway function; and

(b) training said animal under conditions sufficient to stimulate neuronal activity or a pattern of neuronal activity in said animal.

19. The method of any one of Claims 1, 2, 6, 7, 9, 11, 13, 15, 17 and 18 wherein said animal has undergone neuronal stem cell manipulation.

20. A method of therapy of a cognitive deficit associated with a central nervous system disorder or condition in an animal having undergone neuronal stem cell manipulation comprising the steps of:

(a) administering to said animal an augmenting agent which enhances CREB pathway function; and

(b) training said animal under conditions sufficient to stimulate neuronal activity or a pattern of neuronal activity in said animal.

21. The method of Claim 20 wherein training in step b) further produces an improvement in performance by said animal of a cognitive task whose deficit is associated with said central nervous system disorder or condition.

22. The method of any one of Claims 1, 2, 6, 7, 9, 11, 13, 15, 17 and 21 wherein a performance gain is achieved relative to the performance of said cognitive task or said specific aspect of cognitive performance achieved by training alone.

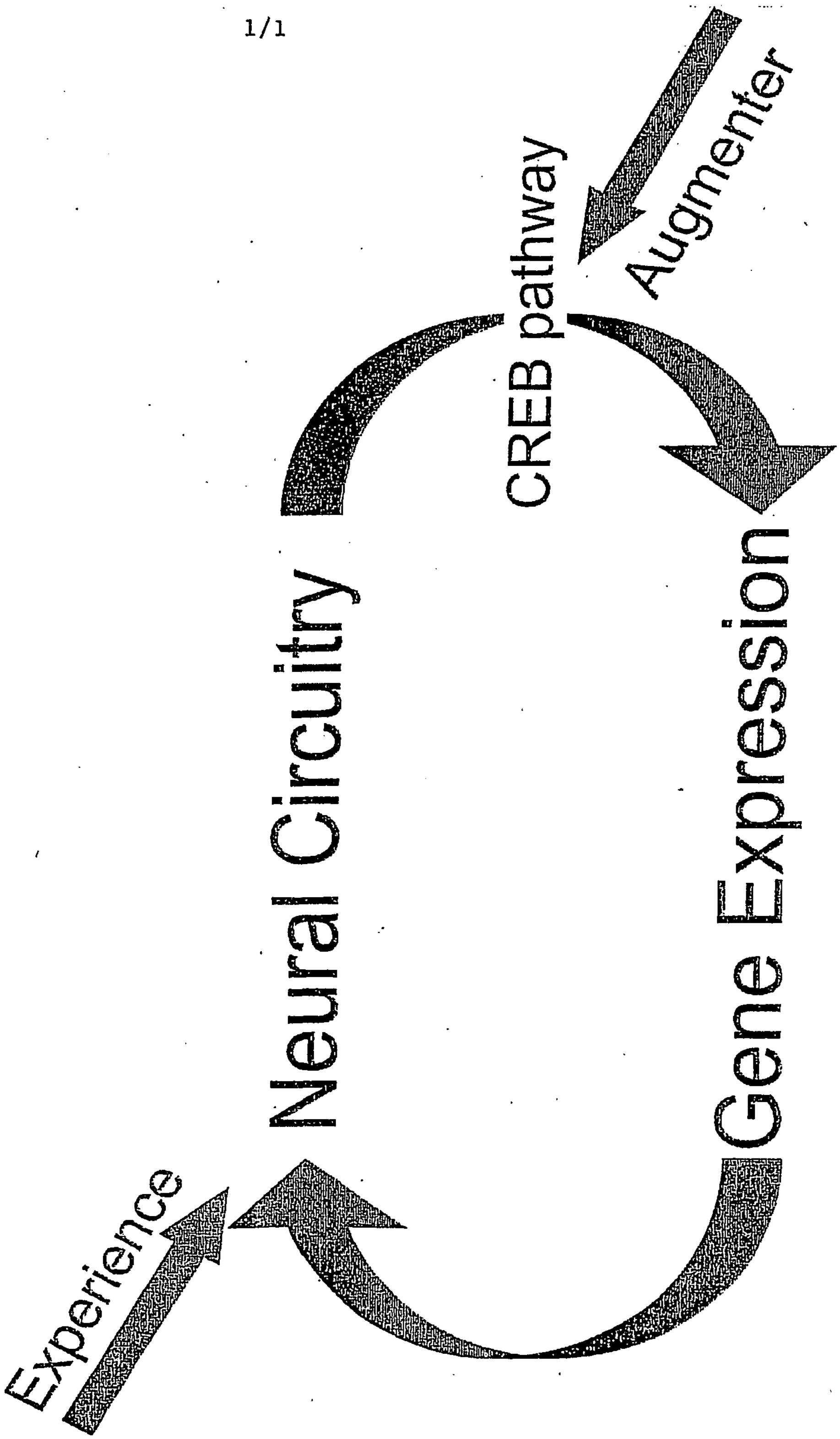
23. The method of any one of Claims 1, 2, 6, 7, 9, 11, 13, 15, 17, 18 and 20 wherein in step b), training comprises multiple training sessions, and optionally said augmenting agent is administered before and during each training session.

24. The method of any one of the preceding Claims wherein said animal is a mammal, for example a human.

25. The method of any one of Claims 6, 7, 9, 11, 13, 15, 17, 18 and 29 wherein said augmenting agent induces CREB-dependent gene expression.

26. An augmenting agent which enhances CREB pathway function, for use in therapy, for example in a method according to any one of Claims 1 to 25.

27. Use of an augmenting agent which enhances CREB pathway function, for the manufacture of a medicament for use in a method according to any one of Claims 1 to 25.


Augmenter
CREB pathway
Neural Circuitry
Gene Expression
Experience

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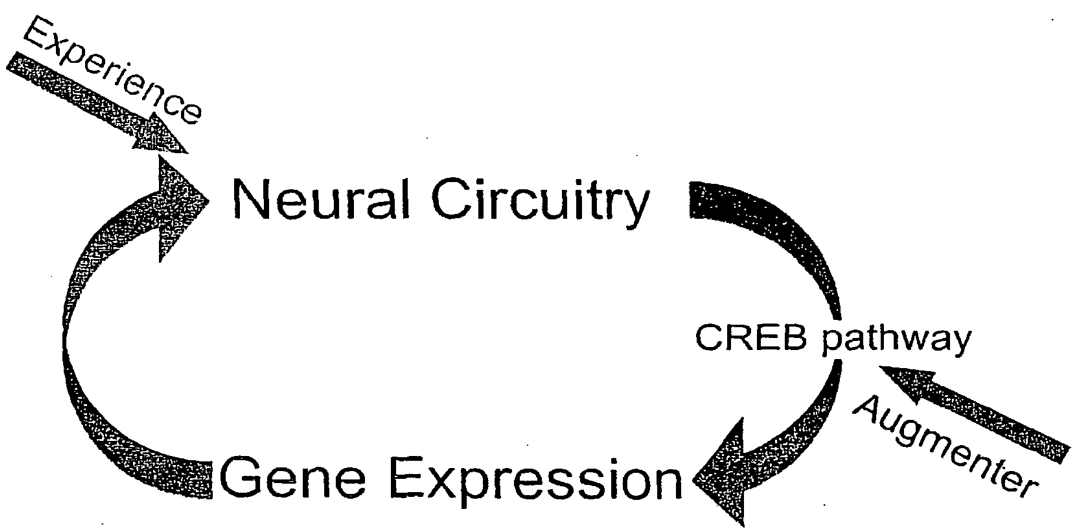
(54) Title: AUGMENTED COGNITIVE TRAINING



(57) Abstract: The present invention provides methods of therapy of cognitive deficits associated with a central nervous system disorder or condition, methods of enhancing cognitive performance and methods for repeated stimulation of neuronal activity or a pattern of neuronal activity, such as that underlying a specific neuronal circuit(s). The methods comprise combining cognitive training protocols and a general administration of CREB pathway-enhancing agents.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.C.P. YIN ET AL.: "CREB as a memory modulator: Induced expression of a dCREB2 activator isoform enhances long-term memory in Drosophila." CELL, vol. 81, 7 April 1995 (1995-04-07), pages 107-115, XP002205609 CAMBRIDGE, MA, US cited in the application	1-27
Y	page 109, right-hand column, paragraph 2 page 111, left-hand column, line 9 - line 14 page 111, left-hand column, line 21 - line 25	1-25

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
11 July 2002	26/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ryckebosch, A

International Application No
PCT/US 01/25048

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 11270 A (TULLY TIMOTHY P ;COLD SPRING HARBOR LAB (US); REGULSKI MICHAEL (US) 18 April 1996 (1996-04-18) cited in the application	1-27
Y	page 13, line 1 - line 18; figure 15B page 26, line 32 -page 27, line 5 page 31, line 2 - line 22; example 9 ---	1-25
X	B. MILNER ET AL.: "Cognitive neuroscience and the study of memory." NEURON, vol. 20, 1998, pages 445-468, XP002205610 CAMBRIDGE, MA, US	1-27
Y	page 457, right-hand column, last paragraph -page 458, left-hand column, paragraph 1 ---	1-25
X	L. BEVILAQUA ET AL.: "Drugs acting upon the cyclic adenosine monophosphate/protein kinase A signalling pathway modulate memory consolidation when given late after training into rat hippocampus but not amygdala." BEHAVIOURAL PHARMACOLOGY, vol. 8, no. 4, August 1997 (1997-08), pages 331-338, XP008005667 LONDON, GB	26,27
Y	page 331, left-hand column, line 1 -page 332, left-hand column, paragraph 2; figure 2 page 332, right-hand column, paragraph 2 page 335, left-hand column, paragraph 2 page 335, right-hand column, line 3 -page 336, left-hand column, line 6 ---	1-25
X	M.E. BACH ET AL.: "Age-related defects in spatial memory are correlated with defects in the late phase of hippocampal long-term potentiation in vitro and are attenuated by drugs that enhance the cAMP signaling pathway." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 96, April 1999 (1999-04), pages 5280-5285, XP002205611 WASHINGTON, US	26,27
Y	page 5285, left-hand column, line 6 - last line -----	1-25

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US 01/25048

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-27 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-27 (all partially)

Present claims 1-27 relate to the use of compounds defined by reference to a desirable characteristic or property, namely the use of compounds which enhance CREB pathway function.
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned specifically in the description at page 17, line 24 to page 19, line 8, such as: 8-bromo cAMP, forskolin, thapsigargin, rolipram, IBMX, exogenous CREB, CREM and ATF-1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/25048

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9611270 A	18-04-1996	US 5929223 A	27-07-1999
		US 6051559 A	18-04-2000
		CA 2202087 A1	18-04-1996
		EP 0781335 A1	02-07-1997
		JP 10507348 T	21-07-1998
		WO 9611270 A1	18-04-1996